REVIEW

Managing the Diabetic Patient with Acute Myocardial Infarction

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The diabetic patient has a substantially increased in-hospital mortality after acute myocardial infarction, which is around twice that of non-diabetic subjects. A number of interventions can substantially improve this outcome. The use of thrombolytic therapy reduces case fatality proportionately to a similar degree to that in non-diabetic patients, but because of the higher background risk, absolute benefits are substantially greater. In the world literature, there is just one reported case of intraocular haemorrhage after thrombolysis in a diabetic patient, and that resolved in 3 weeks, meaning that anxieties around theoretical adverse effects of thrombolysis should not preclude its use. There is no evidence regarding the advantages of any one thrombolytic agent in these subjects. Aspirin treatment again has similar benefits to those in non-diabetic subjects, and should be administered at presentation. Some evidence suggests that a higher dose of aspirin should be used in diabetic, compared to non-diabetic, patients. Finally, the DIGAMI Study has shown that insulin and glucose infusion during the hospital admission, followed by multiple injection therapy thereafter, reduces mortality by around one-third, both at 12 months and at around 3½ years. Whether these advantages are because of improved early or late glycaemic control, or because of withdrawal of sulphonylureas, is still unclear, but this uncertainty should not stand in the way of introducing policies for insulin infusion in all diabetic patients admitted with acute myocardial infarction. © **1998 John Wiley & Sons, Ltd.**

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Introduction

The diagnosis of diabetes brings with it a substantial amount of baggage. For the newly diagnosed patient, a previously carefree existence becomes one burdened with tablets or injections, urine tests or fingerpricks. Diabetes can make you go blind, need a kidney machine, or lose a toe or a foot. But the Sword of Damocles, suspended over the person with diabetes, is engraved with the words 'Coronary Heart Disease'. Largely as a result of this one category of disease, the newly diagnosed patient with diabetes still has a life expectancy of around two-thirds that of a non-diabetic person of the same age.[1]

Diabetic patients and their carers have for years conspired to concentrate on 'control'. The UK Prospective Diabetes Study[2] will at last provide the definitive answer as to whether intervening to reduce glycaemic exposure has any part to play in the excess risk of coronary heart disease (CHD) in people with diabetes, although observational studies suggest, at best, a fairly small influence of blood glucose.[3,4] In the interim, meta-analysis of intervention trials in non-diabetic patients,[5,6] and subgroup analyses of diabetic subjects in these trials of blood pressure and cholesterol lowering,[7,8] have provided estimates of potential gains in life expectancy, or of Numbers Needed to Treat per event prevented, in diabetic patients.

The increase in CHD mortality in diabetic patients is sometimes considered synonymous with an increased risk of atherosclerosis. Clearly, the atherosclerotic plaque is necessary for the development of CHD, but it is not sufficient. The complicated plaque, which precipitates the acute myocardial infarction (AMI), is one which either has ruptured or has developed thrombus on an inflamed or eroded surface.[9] Thus inflammation and thrombosis, superimposed on the atherosclerotic plaque, are important contributors to the acute event. Furthermore, the acute event and its outcome also plays an important role in determining CHD mortality in epidemiological terms. The diabetic patient has a substantially worse outcome after an AMI than does a person without diabetes, with an approximately twofold increase in case fatality during the hospital stay.[10,11] In our hospital during the 1980s, we found that as many as 42 % of the diabetic patients admitted with AMI died during their hospital stay, compared with 25 % of the non-diabetic infarct patients.[10] The excess risk is almost

Abbreviations: AMI acute myocardial infarction, CHD coronary heart disease

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entirely attributable to left ventricular dysfunction—cardiogenic shock or left ventricular failure—despite the fact that the infarct size is generally no larger in the diabetic than in the non-diabetic patient.[11] The evidence suggests that, despite overall improvements in outcome of AMI, the excess risk of the diabetic patient has persisted into the thrombolytic era.[12–15] It can be calculated, indeed, that the excess case fatality from the acute event makes a contribution to the total excess mortality of diabetic patients that is similar to the increased risk of suffering the AMI in the first place.[16] This fact has important implications for practising acute physicians, as it implies that their role in reducing CHD mortality is as important as that of the general practitioner and the diabetic clinic doctor, who concentrate on primary prevention by risk factor reduction. Furthermore, this role is expanded by the fact that major benefits of several approaches to secondary prevention have been shown for diabetic patients after recovery from a myocardial infarct.

This review will consider certain aspects of the in-hospital management of the diabetic patient with an AMI—thrombolytic therapy, aspirin, and glycaemic control. Because there is little or no information about other aspects of management of AMI in the diabetic patient, including heparin[17] and magnesium,[18] these will not be further discussed. Other treatments which may be initiated during the in-hospital stay, but are more related to secondary prevention rather than reducing the mortality from the acute event, will be covered in the accompanying article. These interventions include lipid lowering drugs, angiotensin converting enzyme inhibitors, and beta blockers.

Thrombolytic Therapy

The advent of thrombolysis has had a major impact on cardiological practice in terms of reducing mortality. But the other major impact is that on evidence-based practice: the trials of thrombolytic therapy were among the first large scale intervention studies in which adequate numbers of patients were randomized to permit quantitation of benefit and risk.[19–23] In these large intervention studies, diabetic patients comprised some 10 % or more of all subjects randomized, the higher prevalence than in the general population reflecting both the age of the subjects under study and the additional cardiovascular risk of the diabetic patient. Yet even this proportion of diabetic subjects in a study of tens of thousands of patients was generally insufficient to demonstrate significant benefit in this subgroup. In consequence, the advent of meta-analytical techniques,[24] permitting amalgamation of data on particular groups from several studies, was necessary to show that there was nothing peculiar about the diabetic patient with a myocardial infarction (Figure 1). In terms of *proportionate* benefit, the reduction in 35 day mortality with thrombolysis is similar in diabetic and non-diabetic patients. However, this needs to be considered in conjunction with the

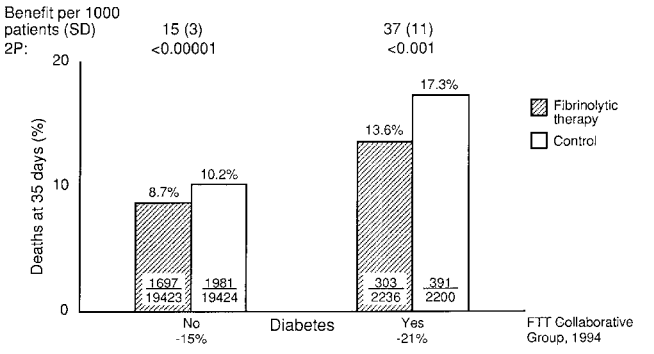

Figure 1. The benefits of thrombolytic therapy on 35-day mortality in non-diabetic and diabetic subjects[24]

excess in *absolute* 35 day mortality of diabetic patients. The consequence is that thrombolytic therapy for diabetic patients is of greater absolute benefit than for non-diabetic patients in terms of numbers of lives saved per treatment.[25]

It is clear, however, that the use of thrombolytic therapy in diabetic patients is less widespread than it could be.[26,27] Recent series have shown some improvement,[28] although the ability of such studies to represent universal practice is uncertain. One feature of importance in considering the use of thrombolysis is the presence of proliferative retinopathy. The presence of untreated proliferative retinopathy had been considered as a contraindication to thrombolytic therapy, because of the risk of bleeding from retinal new vessels, with this recommendation being included in a number of data sheets.[25] It is clear, however, that this risk had been based on theory rather than practice.[25] A review of the literature was able to find only one case of retinal haemorrhage in a diabetic patient given thrombolytic therapy, which resulted in a 3-week period of visual deterioration.[29] The GUSTO Study included 6011 diabetic patients who were given thrombolysis, and in only one case was any ocular complication noted—a periorbital haematoma.[30] As can be calculated from Figure 1, administering thrombolytic therapy to 1000 diabetic patients would result in 37 fewer deaths at 35 days. Set against this, the risk of visual deterioration appears negligible. The logic would be at least to offer the option to the patient if s/he were well enough.

Despite the parallel efficacy of thrombolysis on 35-day survival in diabetic and non-diabetic patients, some angiographic or enzyme release studies suggest the coronary artery thrombus of the diabetic patient is more resistant to thrombolytic therapy than that of non-diabetic patients,[31,32] perhaps related to the higher concentrations of the inhibitor of fibrinolysis, plasminogen activator inhibitor-1.[32] However, in the GUSTO Study, the 90 minute patency rate was similar for diabetic and non-diabetic subjects.[30] There are suggestions from a small study that elderly diabetic patients are at excess risk of haemorrhagic complications from thrombolysis,[33] but an analysis of some 7000 diabetic and 43 000 non-diabetic

patients treated with thrombolysis showed that complication rates were similar in the two groups.[13,30] Data from the overviews of thrombolytic therapy do not support suggestions of differences in benefit of different agents in the general population,[24,34] and numbers are insufficient to make such comparisons in diabetic subpopulations. It is possible, however, that newer thrombolytic agents may play a role in future.

Aspirin

Debate has raged about the use of aspirin in diabetic patients. In the ISIS-2 study, the 35-day mortality in all subjects was reduced to a similar degree by streptokinase and by aspirin, commenced on admission with 165 mg.[20] However the subgroup analysis of diabetic subjects in this study found a significant interaction, implying that they did not benefit from aspirin. The trialists expressed caution in interpreting data from multiple subgroups, in that such analyses frequently throw up spurious positive and negative results by chance alone, as exemplified by the lack of apparent benefit from aspirin in patients born under the star signs Gemini or Libra.[20,35] Other major thrombolytic studies, and other investigations of aspirin use in at risk patients with diabetes, show similar benefit to that in non-diabetic subjects (Figure 2),[36,37] even though some reports suggest that diabetic patients need a higher dose of aspirin than do patients without diabetes.[38] It would appear logical to initiate aspirin treatment with thrombolytic therapy in diabetic patients, and continue in a dose of 300 mg daily of enteric coated aspirin long term.[37]

Glycaemic Control

The role of glycaemic control in reducing the risk of large vessel disease in diabetic patients remains unresolved. Observational studies suggest that poorly controlled patients tend to suffer more cardiovascular events,[3,4] but intervention studies, in both Type 1 and Type 2 diabetes, have provided conflicting answers. Thus the UGDP Study suggested a potentially harmful effect of improved control with sulphonylureas or phenformin,

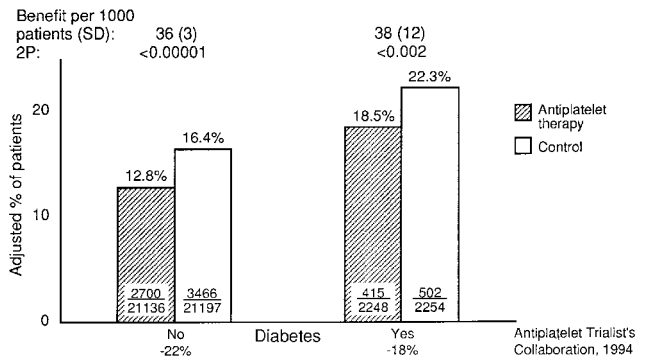

Figure 2. The benefits of aspirin on cardiovascular events in non-diabetic and diabetic subjects[36]

and no benefit of that with insulin.[39] The DCCT, in Type 1 diabetic patients, found a not quite significant reduction in all macrovascular events in the intensified therapy group, but the age of the study population precluded any expectation of answers to questions of macrovascular benefit.[40] In terms of *primary* cardiovascular prevention, the possible benefits of tight control await the findings of the UK Prospective Diabetes Study, due to report this year.[2]

In the context of a myocardial infarction, clear evidence exists now. The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study has shown a major advantage of improved glycaemic control during and after myocardial infarction. In this study, 620 patients with known or newly diagnosed diabetes, and plasma glucose concentration exceeding 11 mmol l^{-1}, were randomized to receive either an intensified insulin-based regimen, or hypoglycaemic therapy at the discretion of the physician.[41] The intensified regimen comprised the use of insulin and glucose infusion in hospital (Table 1), followed by multiple injection insulin treatment for at least 3 months. Glycaemic control was significantly improved at 24 hours and at discharge in the infusion group (Table 2). Although there was no significant difference in in-hospital deaths, the 12 month mortality was reduced by 30 %,[41] and that at a mean follow-up of 3.4 years was reduced by 28 % in the infusion group.[42] The anxieties about possible

Table 1. Protocol used by the coronary care unit nurses for the insulin-glucose infusions

Infusion: 500 ml 5 % glucose with 80 IU of soluble insulin (~1 IU 6 ml^{-1}).

Start with 30 ml h^{-1}. Check blood glucose after 1 h. Adjust infusion rate according to the protocol and aim for a blood glucose level of 7–10 mmol l^{-1}. Blood glucose should be checked after 1 h if infusion rate has been changed, otherwise every 2 h. If the initial decrease in blood glucose exceeds 30 %, the infusion rate should be left unchanged if blood glucose is >11 mmol l^{-1} and reduced by 6 ml h^{-1} if blood glucose is within the targeted range of 7 to 10.9 mmol l^{-1}.

If blood glucose is stable and ≤10.9 mmol l^{-1} after 10 pm, reduce infusion rate by 50 % during the night.

Blood glucose level (mmol l^{-1})	
>15	Give 8 IU of insulin as an intravenous bolus injection and increase infusion rate by 6 ml h^{-1}.
11 to 14.9	Increase infusion rate by 3 ml h^{-1}.
7 to 10.9	Leave infusion rate unchanged.
4 to 6.9	Decrease infusion rate by 6 ml h^{-1}.
<4	Stop infusion for 15 min. Then test blood glucose and continue testing every 15 min until blood glucose is ≥7 mmol l^{-1}. In the presence of symptoms of hypoglycaemia, administer 20 ml of 30 % glucose intravenously. The infusion is restarted with an infusion rate decreased by 6 ml h^{-1} when blood glucose is ≥7 mmol l^{-1}.

Table 2. Benefits of intensive insulin treatment in diabetic patients with acute myocardial infarction

	Control group	Infusion group	*P* valve
Numbers	314	306	
Blood glucose			
at 24 h (mmol l^{-1})	11.7 (4.1)	9.6 (3.3)	<0.0001
at discharge (mmol l^{-1})	9.0 (3.0)	8.2 (3.1)	<0.01
Reduction in HBA_{1c} at 12 months (%)	0.4 (1.8)	0.9 (1.9)	<0.01
Proportion on insulin			
at discharge	135 (43 %)	266 (87 %)	<0.0001
at 1 year	141 (49 %)	220 (72 %)	<0.0001
Mortality			
at 1 year	82 (26 %)	58 (19 %)	0.027
at end of follow-up (mean 3.4 years)	138 (44 %)	102 (33 %)	0.011

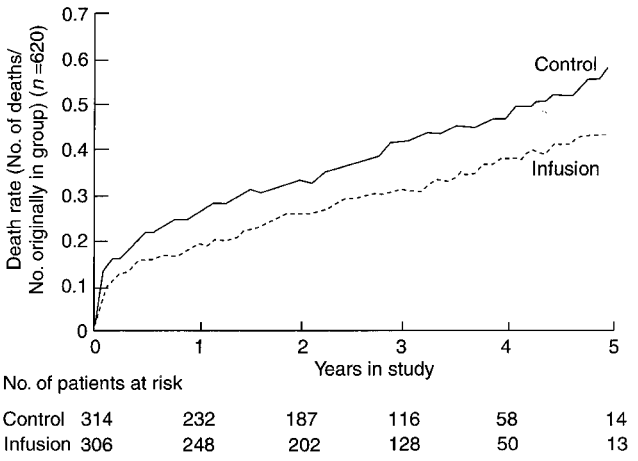

Figure 3. Actuarial mortality curves during long-term follow-up in hyperglycaemic patients receiving either insulin and glucose infusion or acting as controls from the DIGAMI Study. Reproduced from Malmberg/DIGAMI Study Group[42] by kind permission of the *British Medical Journal*

risks of hypoglycaemia in the post-infarct patient are laid to rest by the observation that 15 % of intensified therapy patients had a hypoglycaemic event, compared to none in the control group, but without adverse consequences.

Is this proof that tight glycaemic control around the time of the infarct improves outcome? It is not quite so simple. Nearly three-quarters of the infusion group were still on insulin at 12 months, compared to less than half the control group, with continuing improvement in glycaemic control (Table 2). The authors have no information regarding subsequent therapy, but suspect that few patients would have come off insulin after a year of treatment. Thus it remains unanswered whether the benefit accrued from insulin infusion *during* the acute event, from improved glycaemic control *following discharge*, or from a pharmacological benefit of *withdrawing oral hypoglycaemic agents*. The DIGAMI Study is one of *secondary* prevention. The distinction is important, as the process of reinfarction may be more a consequence of procoagulant, rather than proatherogenic, mechanisms. The observation that mortality curves in the two groups continued to diverge after discharge (Figure 3)[41,42] could be interpreted to imply reduced risk of rethrombosis, perhaps consequent on the effects of improved glycaemic control, or on the direct influence of insulin, as opposed to sulphonylurea, therapy on procoagulant mechanisms.[43] There are, however, other potential theoretical benefits for insulin in high risk patients. Most sulphonylureas close the K_{ATP} channel both in the pancreatic beta cell and in the cardiac myocyte, and may thereby have potentially harmful effects in the post-infarct setting, impairing the process of ischaemic preconditioning.[44] The DIGAMI investigators performed an interesting subgroup analysis, which showed that the greatest proportional benefit in the study was for those subjects previously not treated with insulin, and otherwise at low risk because of age and prior history.[42] While these observations hint at a potential adverse effect from sulphonylureas, it would be risky to over-interpret the data, or to over-inflate the potential benefits from the new and more pancreas-specific sulphonylureas now available. Once again, the UKPDS should answer the point as to whether there is any adverse cardiovascular effect of the sulphonylureas. Furthermore, the ongoing DIGAMI 2 Study may enable the component parts of the intervention to be separated.

The DIGAMI Study, as a secondary prevention study in a high risk group of patients, provides evidence about an intervention requiring small Numbers Needed to Treat to prevent adverse outcomes. In the follow-up of the DIGAMI Study, this number can be calculated as 11 patients to be treated with insulin to prevent 1 death at 3.4 years.[42] The findings are important enough to influence the way we should all be treating diabetic patients with myocardial infarction: they should be started on an insulin and glucose infusion on admission, and be continued on multiple injection insulin therapy indefinitely after discharge.

For the time being, the DIGAMI Study also answers the question as to what approach should be taken for the patient admitted with acute myocardial infarction who is hyperglycaemic (plasma glucose >11 mmol l^{-1}) but without previously known diabetes. Such a patient is at substantially elevated risk of dying during the hospital stay,[45,46] again mainly from pump failure. However, analysis of levels of glycated haemoglobin in such patients would suggest that only around one-fifth have previously undiagnosed diabetes, the remainder having stress hyperglycaemia. Hyperglycaemic patients without previously diagnosed diabetes represented 13 % of all patients admitted in the DIGAMI Study, and were randomized in the same fashion as those with known diabetes. As these patients were not analysed separately, the implication is that for the present such patients should also be treated with insulin infusion.

Conclusions

The diabetic patient with a myocardial infarction is a high risk patient in an even higher risk setting. The proven benefit of a number of interventions for the acute event, in a population at such high risk, implies major advantages in terms of absolute gains in life expectancy. And the fact that these interventions have a greater benefit-to-cost ratio than in a lower risk, non-diabetic population, should imply that here, at least, is one move towards St Vincent Declaration targets which should be supported alike by diabetologists, cardiologists, health economists, and health service managers.

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